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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/755,166	01/09/2004	Muthiah Manoharan	ISIS-5425	1276

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EXAMINER	
RILEY, JEZIA	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 05/26/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/755,166	MANOHARAN ET AL.	
	Examiner	Art Unit	
	Jezia Riley	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 45-50 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 45-50 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 2/17/04.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

S.O.O.

DETAILED ACTION

Double Patenting

1. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

2. Claims 45-50 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 21 of U.S. Patent No. 6,153,737. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are both claiming a compound comprising a plurality of linked nucleoside wherein at least one of the nucleosides is a 2'-deoxy-2'-fluoro, 2'-O-C1-C20 alkyl, 2'-O-C2-C20 alkenyl, 2'-O-C2-C20 alkynyl, 2'-S-C2-C20 alkyl, 2'-S-C2-C20 alkenyl, 2'-S-C2-C20 alkynyl, 2'-NH-C2-C20 alkyl, 2'-NH-C2-C20 alkenyl, 2'-NH-C2-C20 alkynyl nucleoside; and at least one the nucleosides is a 5' terminal having a lipophilic molecule linked to the 5'-position of the nucleoside. In the patent the peptide, protein, vitamin for example are viewed to be inclusive of the non aromatic lipophilic molecules of the instant claims.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 45-50 are rejected under 35 U.S.C. § 103 as being unpatentable over Huie et al, (Patent # 5,470,967), in view of Smith et al. (Patent # 5,015,733).

Huie et al. provide a compound having a formula shown in col.4 where the 2'-substituent can be a hydrogen alkoxy, or halogen, or protective group. The phosphate backbone can be phosphodiester or a modified phosphate backbone such as phosphorothioate, phosphorodithioate or alkylphosphonate.

Smith et al. teach a versatile and general method, permitting amino group to be selectively placed at any position on oligonucleotides of any composition or length which is attainable by current DNA synthetic methods. Fluorescent dyes or other

detectable moieties may be covalently attached to the amino groups to yield the corresponding oligonucleotide (see abstract). These groups may be selectively inserted at any desired position in the oligonucleotide. They are readily and specifically reacted with a variety of amino reactive functionalities, and thereby permit the covalent attachment of a wide variety of chemical species in a position specific manner. In col. 7-8, bridging paragraph, examples are given, where, R5 as shown in FIG. 5, are either H, OR, or NHR', wherein R and R' are appropriate protecting groups; R is generally a lower alkyl such as methyl, t-butyl, , or a lower alkyl ester, such as acetyl, or an alkyl acetal, such as tetrahydropyranyl, or a silyl ether, such trimethylsilyl or t-butyl-dimethylsilyl, or a sulfonic acid ester, such as methanesulfonyl; R' is any common, standard nitrogen protecting group, such as those commonly used in peptide, this includes, but is not limited to, acid-labile protecting groups such as formyl, t-butyloxycarbonyl, furfuryloxycarbonyl, t-amyloxycarbonyl, adamantyloxycarbonyl; base labile protecting groups such as trifluoroacetyl, 9-fluorenylmethyloxycarbonyl, methylsulfonylethyloxycarbonyl, and 2-cyano-t-butyloxycarbonyl; and others, such as chloroacetyl, acetoacetyl, dithiasuccinoyl, maleoyl, isonicotinyl, 2-bromoethyloxycarbonyl, and 2,2,2-trichloroethyloxycarbonyl. Which are viewed as being inclusive of the non aromatic molecule of instant claim 47. The materials prepared in this fashion are effective in DNA hybridization methods, as illustrated by their use as primers in DNA sequence analysis, and also by a study of their melting behavior in DNA duplex formation (col.5, lines 53-66).

It would have been obvious at the time the invention was made to synthesis compound comprising plurality of linked nucleosides wherein at least one nucleoside is a 2'-deoxy comprising a 2' substituent as taught by Huie and at least a nucleoside is a terminal nucleoside having a molecule as taught by Smith. A number of structural modification approaches to improve the function of oligodeoxynucleotides as anti-sense reagents have been investigated. One class of modification involves the attachment of chemical appendages to the reagent to stabilize the reagent/target duplex or cleave the target at the site of attachment. Acridine derivatives attached via flexible tethers have been shown to improve the thermodynamic stability of the duplex through intercalation. Similarly, oligodeoxynucleotides bearing tethered psoralens can be covalently cross-linked to target following irradiation of the duplex. Cross-linking can also be accomplished through the use of tethered alkylating agents. Cleavage of the target through the use of oligodeoxynucleotides bearing tethered ethylenediaminetetraacetic acid (EDTA)/iron or 1,10-phenanthroline/copper has been demonstrated in vitro. Numerous other attachments for these purposes have been described. Functionalization with poly (L-lysine) which is viewed as a non-aromatic lipophilic molecule, has been employed to improve transport. The attachment of chemical functionalities to the termini of oligodeoxynucleotides can provide enhanced nuclease-resistance in some cases (Huie et al. col.2). Therefore one would have been motivated to synthesize a oligonucleotide where nucleosides have 2' unsubstituted or substituted nucleosides and 5' substituted termini to increase the stability of the duplex against RNaseH and improve the function of oligonucleotides as antisense reagents by modification of chemical appendages.

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jezia Riley whose telephone number is 571-272-0786. The examiner can normally be reached on 9:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Tuesday, May 24, 2005

JEZIA RILEY
PRIMARY EXAMINER